Synthesis of Oxazine-Embedded 1,1′-Biaryl-2,2′-diamine via [3,3]-Sigmatropic Rearrangement of Oxazine Diarylhydrazine

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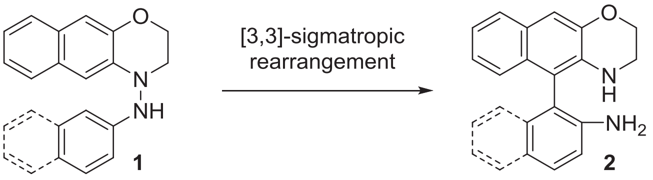
Axially chiral 1,1′-binaphthyl-2,2′-diamine (BINAM) and its derivatives[1] are important chiral ligands and organocatalysts proven to be effective in various asymmetric transformations including epoxide opening,[2a,b] hydrogenation,[2c] hydroamination,[2d] carbosulfenylation,[2e] conjugate addition,[2f] domino-Michael–aldol,[2g] and Diels–Alder reaction[2h]. As with BINOL (1,1′-bi-2-naphthol) or BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene), bulky aryl substituents at 3,3′-positions of BINAM proved to enhance stereoselectivity. Literature survey revealed only a few synthetic methods, most of which rely on a directed *ortho*-lithiation/halogenation followed by Pd-catalyzed coupling or a Pd-catalyzed direct C—H arylation, among other less efficient ones.[2c,d,3] However, installation of the bulky aryl groups is by no means straightforward and often requires hazardous reagents, harsh reaction conditions, or low yielding lengthy steps. Such difficulties together with lack of a reliable method to the BINAM core hamper further development of BINAM-derived chiral ligands and organocatalysts. As a part of our ongoing study on aryl hydrazides,[4] we have envisioned the oxazine unit incorporated in the 1,1′-biaryl-2,2′-diamines **2** could provide the required steric bias for effective stereocontrol. Prompted by their potentials as new chiral ligands and organocatalysts, we set out to investigate the synthesis of oxazine-embedded 1,1′-biaryl-2,2′-diamine **2** by using [3,3]-sigmatropic rearrangement of diarylhydrazines **1** (Scheme 1).[4d,k,5]

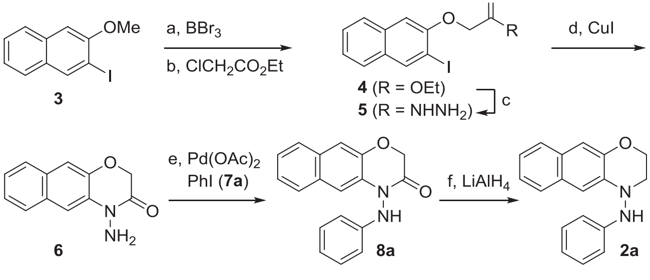
The present study was commenced by the preparation of diarylhydrazine **2a** from 2-iodo-3-methoxy-naphthalene (**3**) (Scheme 2).[6] BBr$_3$-mediated demethylation followed by the reaction with ethyl chloroacetate furnished acetate **4**, which on gentle heating with hydrazine hydrate yielded aryl hydrazide **5** in good overall yield. Intramolecular Cu-catalyzed C—N coupling reaction gave cyclic hydrazide **6** in 79% yield. The C—N coupling reaction with iodobenzene afforded diaryl hydrazide **8a** in 65% yield. The reduction of the lactam carbonyl group was achieved with LiAlH$_4$ on heating in tetrahydrofuran (THF) under reflux to provide diarylhydrazine **2a**.[7]



Scheme 1. Synthetic plan to 1,1′-biaryl-2,2′-diamine.

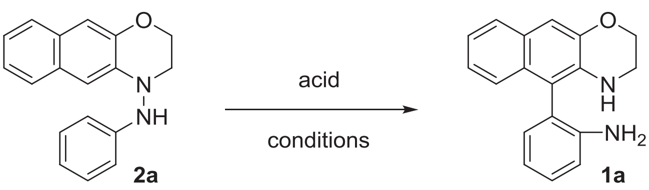
The [3,3]-sigmatropic rearrangement of diarylhydrazine **2a** was investigated under various reaction conditions (Table 1). In these experiments, the reactions were carried out in a dilute premixed acid solution. When stirred in EtOH with 1.2 equiv HCl at room temperature, the reaction gave diamine **1a** in 71% yield (entry 1). Lowering the reaction temperature to 0°C gave much cleaner reactions (entries 2 and 3). With 1.2 equiv of HCl, the reaction gave 83% yield after 12 h. The reaction time was shortened to 30 min with a slightly higher product yield of 89% in the presence of excess HCl (20 equiv). Use of a weaker acid resulted in slower reaction (entry 4).

With optimal reaction conditions in hand, various other oxazine diarylhydrazines were prepared. Iodobenzene with electron-withdrawing substituent was not considered because of potential incompatibility with the ensuing LiAlH$_4$ reduction conditions (Table 2). When subjected into the conditions used for **8a**, hydrazide **6** gave oxazine diaryl hydrazides **8b–8f** mostly in good yield. The resulting diaryl hydrazides were then reduced to set the stage for the [3,3]-sigmatropic rearrangement reactions. In all cases except **8e** (21% for the reduction to **2e**, entry 4), the reduction and rearrangement reactions well proceeded to give 1,1′-biaryl-2,2′-diamines **1b–1f** in good overall yields.



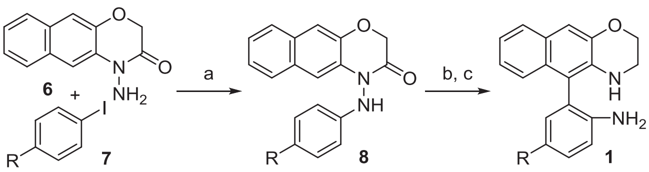
Scheme 2. Reaction conditions: (a) BBr$_3$, methylene chloride, room temperature, overnight, 91%; (b) ClCH$_2$CO$_2$Et, K$_2$CO$_3$, dimethylformaldehyde, 115°C, 2 h, 99%; (c) hydrazine hydrate, MeOH, 40°C, 24 h, 90%; (d) CuI, 1,10-phenanthroline, Cs$_2$CO$_3$, DMF, 80°C, 2 h, 79%; (e) iodobenzene, Pd(OAc)$_2$, [(tBu)$_3$P]HBF$_4$, Cs$_2$CO$_3$, tol, 110°C, 24 h, 65%; (f) LiAlH$_4$, THF, reflux, 24 h, 89%.

Table 1. Model study under various conditions.



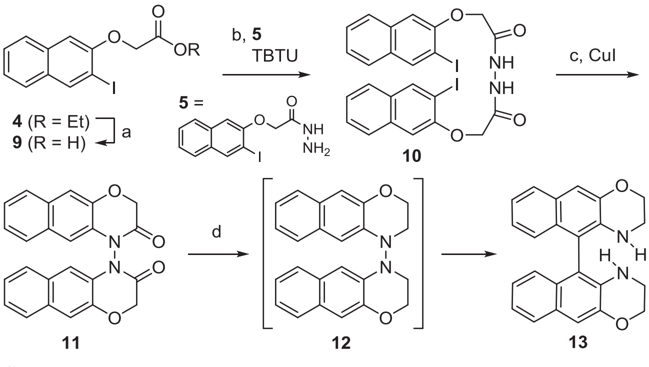
Entry	Acid (equiv)	Conditions	Yield (%)
1	HCl (1.2)	EtOH, room temperature, 1 h	71
2	HCl (1.2)	EtOH, 0°C, 12 h	83
3	HCl (20.0)	EtOH, 0°C, 0.5 h	89
4	H_3PO_4 (5.0)	EtOH, room temperature, 22 h	66

Table 2. Preparation and [3,3]-sigmatropic rearrangement.



Entry	R	**8** (Yield %)	**2** (Yield %)	**1** (Yield %)
1	Me	**8b** (81)	**2b** (97)	**1b** (83)
2	*t*Bu	**8c** (80)	**2c** (95)	**1c** (80)
3	*n*Hex	**8d** (81)	**2d** (95)	**1d** (81)
4	MeO	**8e** (68)	**2e** (21)	**1e** (79)
5	Ph	**8f** (83)	**2f** (99)	**1f** (82)

a: $Pd(OAc)_2$, $[(tBu)_3PH]\ BF_4$, Cs_2CO_3, tol, 110°C, 24 h; b: $LiAlH_4$, THF, reflux, 24 h; c: 0.1 M HCl in EtOH, 0°C, 0.5 h.



Scheme 3. Reaction conditions: (a) 30% KOH (aq), MeOH, room temperature, 1 h, 82%; (b) *N*,*N*,*N*',*N*'-tetramethyl-*O*-(benzotriazol-1-yl)uranium tetrafluoroborate, 2,6-lutidine, **5**, DCM, room temperature, 19 h, 99%; (c) CuI, 1,10-phenanthroline, Cs_2CO_3, DMF, 80°C, 48 h, 93%; (d) $LiAlH_4$, THF, 75°C, 27 h.

We then turned our attention to the synthesis of BINAM **13** with two flanking oxazine units (Scheme 3). Toward this, ester **4** was hydrolyzed to acid **9** for the coupling with hydrazide **5** to afford diaryl hydrazide **10**. Subsequent C—N coupling reaction gave **11** in 93% yield. Reaction with $LiAlH_4$ in THF under reflux implemented both reduction and [3,3]-sigmatropic rearrangement to directly provide BINAM derivative **13** in 72% total yield.

In summary, diarylhydrazine with oxazine unit(s) undergoes [3,3]-sigmatropic rearrangement to give novel oxazine-embedded 1,1′-biaryl-2,2′-diamine in good yield.

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